REMARKS

The Amendments

Claim 1 has been amended to recite, *inter alia,* chemically modified double stranded short interfering ribonucleic acid (siRNA) molecule; (*see, inter alia*, specification page 7, lines 15-28); the antisense strand of said siRNA molecule comprises about 18 to about 27 nucleotides that are complementary to a cholinergic receptor muscarinic 3 (CHRM3) nucleotide sequence comprising SEQ ID NO:305 (*see, inter alia*, page 10, lines 14-19; page 11, lines 14-20) the sense strand of the siRNA molecule comprises a portion of the CHRM3 nucleotide sequence of about 18 to about 27 nucleotides (*see, inter alia,* page 11, lines 14-20) and between about 50 and about 100 percent of the nucleotide positions in one or both strands of the siRNA molecule are chemically modified and the antisense strand of the siRNA molecule comprises about 5, 6, 7, 8, 9, 10 or more 2'-O-methyl nucleotides (*see, inter alia*, page 13, lines 14-28, page 32, lines 2-5, Figures 4 and 5 and descriptions thereof).

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

Priority

The Office asserts that the instant application has an effective filing date of February 20, 2003, the filing date of PCT/US03/05028. Applicants respectfully disagree.

The Office asserts that the statement of priority of application 60/363,124 does not provide a link to PCT/US03/05028, but rather provides a link to the instant application, which was not filed within one year of the US Ser. No.60/363,124.

The instant application claims priority to, *inter alia*, U.S. Patent Application No. 10/757,803, filed January 14, 2004, which is a continuation-in-part of U.S. Patent Application No. 10/720,448, filed November 24, 2003, which is a continuation-in-part of U.S. Patent

Application No. 10/693,059, filed October 23, 2003, which is a continuation-in-part of U.S. Patent Application No. 10/444,853, filed May 23, 2003, which is a continuation-in-part of International Patent Application No. PCT/US03/05346, filed February 20, 2003, and a continuation-in-part of International Patent Application No. PCT/US03/05028, filed February 20, 2003, both of which claim the benefit of, *inter alia*, U.S. Provisional Application No. 60/363,124 filed March 11, 2002. The specification of PCT/US03/05028 incorporates by reference the entire specification of U.S. Provisional Application No. 60/363,124. *See,* page 1, paragraph 1 (stating "[t]hese applications are hereby incorporated by reference herein in their entireties, including the drawings."); MPEP §2163.07(b) (stating "[i]nstead of repeating some information contained in another document, an application may attempt to incorporate the content of another document or part thereof by reference to the document in the text of the specification. The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed."). All other applications in the chain of priority incorporate the earlier applications by reference in their entireties. Therefore, there is a link between application 60/363,124 and, *inter alia,* application PCT/US03/05028 because PCT/US03/05028 incorporates application 60/363,124 by reference in its entirety. The instant application is entitled to a priority date of at least March 11, 2002.

Claim Objections

Claims 1, 3, 14, 16, 17, 19-21, 30 and 31 stand as "objected to." Claim 1 has been amended to recite "ribonucleic acid". Claim 1 has also been amended for clarity. Claim 3 has been canceled. Applicants respectfully request withdrawal of the objection to the claims.

Rejection of Claims 1, 3, and 31 Under 35 U.S.C. §102(b)

Claims 1, 3, and 31 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Parrish *et al.* as evidenced by Zhang *et al.* Claim 3 has been canceled. Therefore, the rejection is moot as applied to claim 3. Applicants respectfully traverse the rejection as it applies to claims 1 and 31.

The amended claims recite that the antisense strand of siRNA molecules comprise about 18 to about 27 nucleotides that are complementary to CHRM3 nucleotide sequence comprising SEQ ID NO:305; that the sense strand is complementary to the antisense strand; and that the sense strand of the siRNA molecule comprises a portion of the CHRM3 nucleotide sequence of

about 18 to about 27 nucleotides. Parrish and Zhang do not teach or suggest siRNA molecules that comprises sense and antisense strands that comprise about 18 to about 27 nucleotides that correspond to SEQ ID NO:305, which is a CHRM3 nucleotide sequence. Therefore, Parrish and Zhang do not anticipate claims 1 and 31. Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 1, 3, 14, 16, 17, 19-21, 30 and 31 Under 35 U.S.C. § 103(a)

Claims 1, 3, 14, 16, 17, 19-21, 30, and 31 stand rejected as allegedly obvious over Nyce *et al.,* in view of Parrish *et al.*, Elbashir *et al.*, Pavco *et al.*, Hammond *et al.*, and Caplen *et al.* Claim 3 has been canceled. Therefore, the rejection is moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to claims 1, 14, 16, 17, 19-21, 30 and 31.

The Office relies on Nyce for its teaching of targeting CHRM3 with antisense oligonucleotides, Hammond and Caplen for their teachings regarding siRNA and RNAi, and Elbashir, Parrish, and Pavco for their teachings relating to modifications. However, none of these references, alone or in combination, make obvious the presently claimed constructs in which between 50 and 100 percent of the nucleotide positions in one or both strands of the siRNA molecule are chemically modified and any purine nucleotides present in the antisense strand are 2'-O-methyl purine nucleotides. None of the art, alone or in combination, provides any insight into whether such highly modified double-stranded siRNA nucleic acid constructs would function. Indeed, in a section tellingly entitled, "The siRNA User Guide," Elbashir expressly teaches away from highly modified siRNA constructs:

> "The siRNA User Guide"
>
> Efficiently silencing siRNA duplexes are composed of 21 nt sense and 21 nt antisense siRNAs and must be selected to form a 19 bp double helix with 2 nt 3'-overhanging ends. 2'-deoxy substitutions of the 2 nt 3' overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNAse resistance of siRNA duplexes. **More extensive 2'-deoxy or 2'-*O*-methyl modifications, reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNAP assembly.**

(*see*, page 6885, left col.; emphasis added; see also, Tuschl *et al.* US Pat. Publ. 2004/0259247, paragraphs [0178] to [0179]). Because *the only* teaching in the cited art addressing the issue of

the degree of modifications tolerated in siRNA molecules expressly states that more than a few end modifications should be avoided, it could not have been obvious to make the highly modified constructs now being claimed; the present claims go directly against the express teachings of the art. Consequently, the present claims cannot be obvious over the cited art.

Rejection of Claims 1, 3, 10-12, 14, 16, 17, 19-21, 30 and 31 Under 35 U.S.C. § 103(a)

Claims 1, 3, 10-12, 14, 16, 17, 19-21, 30, and 31 stand rejected as allegedly obvious over Nyce *et al.,* in view of Parrish *et al.*, Elbashir *et al.*, Pavco *et al.*, Hammond *et al.*, and Caplen *et al.*, further in view of Agrawal *et al.* Claims 3, and 10-12 have been canceled. Therefore, the rejection is moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to claims 1, 14, 16, 17, 19-21, 30 and 31.

The Office relies on the teachings of Nyce, Parrish, Elbashir, Pavco, Hammond, and Caplen as described above. The Office relies on the teachings of Agrawal for its teaching of polynucleotide linkers. Agrawal does not correct the deficiencies of the Nyce, Parrish, Elbashir, Pavco, Hammond, and Caplen references as described above. Therefore, this combination of seven references does not teach or suggest the invention. Applicants respectfully request withdrawal of the rejection.

Provisional Double Patenting Rejection

Claims 1, 3, 10-12, 14, 16, 17, 19-21, 30 and 31 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over the claims of co-pending application No. 10/919,866. Applicants will consider the merits of filing a terminal disclaim upon the indication of otherwise allowable claims in this application.

Conclusion

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, he is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

Date: January 24, 2007

/Lisa M.W. Hillman/
Lisa M.W. Hillman Ph.D.
Registration No. 43,673

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, IL 60606

Telephone: 312-913-0001
Facsimile: 312-913-0002